



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2021

Biomolecular condensates at sites of DNA damage: More than just a phase

Spegg, Vincent ; Altmeyer, Matthias

Abstract: Protein recruitment to DNA break sites is an integral part of the DNA damage response (DDR). Elucidation of the hierarchy and temporal order with which DNA damage sensors as well as repair and signaling factors assemble around chromosome breaks has painted a complex picture of tightly regulated macromolecular interactions that build specialized compartments to facilitate repair and maintenance of genome integrity. While many of the underlying interactions, e.g. between repair factors and damage-induced histone marks, can be explained by lock-and-key or induced fit binding models assuming fixed stoichiometries, structurally less well defined interactions, such as the highly dynamic multivalent interactions implicated in phase separation, also participate in the formation of multi-protein assemblies in response to genotoxic stress. Although much remains to be learned about these types of cooperative and highly dynamic interactions and their functional roles, the rapidly growing interest in material properties of biomolecular condensates and in concepts from polymer chemistry and soft matter physics to understand biological processes at different scales holds great promises. Here, we discuss nuclear condensates in the context of genome integrity maintenance, highlighting the cooperative potential between clustered stoichiometric binding and phase separation. Rather than viewing them as opposing scenarios, their combined effects can balance structural specificity with favorable physicochemical properties relevant for the regulation and function of multilayered nuclear condensates.

DOI: <https://doi.org/10.1016/j.dnarep.2021.103179>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-206236>

Journal Article

Published Version

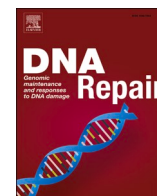


The following work is licensed under a Creative Commons: Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.

Originally published at:

Spegg, Vincent; Altmeyer, Matthias (2021). Biomolecular condensates at sites of DNA damage: More than just a phase. DNA repair, 106:103179.

DOI: <https://doi.org/10.1016/j.dnarep.2021.103179>



Biomolecular condensates at sites of DNA damage: More than just a phase^{☆,☆☆}

Vincent Spegg, Matthias Altmeyer^{*}

Department of Molecular Mechanisms of Disease, University of Zurich, Zurich, Switzerland

ARTICLE INFO

Keywords:

Biomolecular condensates
DNA damage response (DDR)
DNA repair
Genome stability
Liquid-liquid phase separation (LLPS)
Intrinsically disordered regions (IDR)
Low complexity domains (LCD)
Multivalent interactions
Higher-order assemblies

ABSTRACT

Protein recruitment to DNA break sites is an integral part of the DNA damage response (DDR). Elucidation of the hierarchy and temporal order with which DNA damage sensors as well as repair and signaling factors assemble around chromosome breaks has painted a complex picture of tightly regulated macromolecular interactions that build specialized compartments to facilitate repair and maintenance of genome integrity. While many of the underlying interactions, *e.g.* between repair factors and damage-induced histone marks, can be explained by lock-and-key or induced fit binding models assuming fixed stoichiometries, structurally less well defined interactions, such as the highly dynamic multivalent interactions implicated in phase separation, also participate in the formation of multi-protein assemblies in response to genotoxic stress. Although much remains to be learned about these types of cooperative and highly dynamic interactions and their functional roles, the rapidly growing interest in material properties of biomolecular condensates and in concepts from polymer chemistry and soft matter physics to understand biological processes at different scales holds great promises. Here, we discuss nuclear condensates in the context of genome integrity maintenance, highlighting the cooperative potential between clustered stoichiometric binding and phase separation. Rather than viewing them as opposing scenarios, their combined effects can balance structural specificity with favorable physicochemical properties relevant for the regulation and function of multilayered nuclear condensates.

1. Introduction

According to Richard Dawkins' 'The Blind Watchmaker: Why the Evidence of Evolution Reveals a Universe without Design', "biology is the study of complicated things that give the appearance of having been designed for a purpose", whereas "physics is the study of simple things that do not tempt us to invoke design" [1]. Oil droplets in water, from this perspective, could be considered simple things, with no sign of design. Living cells, on the other hand, with their intricate architecture and organizational complexity, are complicated things. As tiny high-precision machines, cells use energy to exert spatio-temporal control over the numerous biochemical reactions that take place every millisecond inside the intracellular space. Compartmentalization is key to such spatio-temporal control, and recent years have seen resurging interest in the biological, chemical and physical principles that govern cellular compartmentalization [2–5].

The cell nucleus is the biggest cellular compartment, a membrane-enclosed organelle and home of the chromosomes and the embedded

genetic code. It comprises various layers of organizational complexity to maintain genome structure and function, including chromatin loops and higher-order chromatin architecture, but also a large number of chromatin-associated and non-associated nuclear proteins and protein complexes, which can form biomolecular condensates and thereby subdivide the nuclear space. Biomolecular condensates can be generally defined as intracellular compartments that lack surrounding membranes but function to concentrate biological molecules, and the term was chosen in part because it provides a link to concepts from condensed matter physics [5]. Such assemblies, despite the absence of a lipid membrane, can be considered physical entities, in which certain molecules are enriched, while others are excluded. Biomolecular condensates can form by different means and have different material properties, ranging from highly dynamic liquid droplets to dense and sometimes irreversible aggregates [6–8]. They can form through stoichiometric binding of molecules to one another, *e.g.* with the chromatin scaffold and histone modifications serving as binding site clusters for cooperative or non-cooperative protein binding, or, at the other end of the spectrum, by

[☆] This Special Issue is edited by Penny A. Jeggo. ^{☆☆} This article is part of the special issue Cutting Edge Perspectives in Genome Maintenance VIII.

^{*} Corresponding author at: Department of Molecular Mechanisms of Disease, University of Zurich, Winterthurerstrasse 190, CH-8057, Zurich, Switzerland.

E-mail address: matthias.altmeyer@uzh.ch (M. Altmeyer).

<https://doi.org/10.1016/j.dnarep.2021.103179>

Received 31 May 2021; Received in revised form 8 July 2021; Accepted 9 July 2021

Available online 14 July 2021

1568-7864/© 2021 The Author(s).

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).